All patients with FLT3 mutant AML should receive midostaurin-based induction therapy: of course (if they are fit for standard induction)

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Dana-Farber Cancer Institute
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Harvard Medical School
Disclosures- Richard M. Stone, MD

- **Consulting relationships:**
  - AbbVie; Agios. Amgen, Argenix (DSMB), Arog, Astellas, Celgene (includes DSMB and steering committee), Fujifilm, Janssen; Jazz, Juno, Karyopharm, Merck, Novartis, Ono, Orsenix, Sumitomo, Pfizer, Roche

- **Securities, employment, promotional activities, intellectual property, gifts, grants**
  - None
Dana-Farber Cancer Institute in Boston

Dana/Mayer Building (Office)

Brigham and Women’s Hospital

Yawkey Center (Clinic)
Overexpression is common

25-30% of cases

5-10%

Both mutations cause spontaneous dimerization, ligand-independent growth, and MPD in murine models.
Mutant FLT3 AML is a bad disease

Background

• Midostaurin (PKC412; N-benzoylstaurosporine) is a potent FLT3 (both ITD and TKD) inhibitor (IC$_{50}$ <10 nM) (also inhibits VEGFR, PKC, KIT, and PDGFR)$^{1,2}$

• Midostaurin specifically inhibits growth of leukemic cell lines made factor independent by transfection of activating FLT3 mutation (ITD or D835Y)$^{2}$

• Midostaurin increased survival in a murine BMT model of FLT3 ITD myeloproliferative disorder $^{3}$

Phase II Trial of PKC412: Clinical Activity (75 mg po TID)

- >50% reduction in BM blasts: 5/20 (25%)
  - 2 patients with <5% blasts; 1 on D 28, 1 on D 60*
- >50% reduction in PB blasts: 14/20 (70%)
- 7 (35%) with clinical benefit:

<table>
<thead>
<tr>
<th>Baseline PB blasts</th>
<th>110K</th>
<th>65K</th>
<th>21K</th>
<th>5K</th>
<th>16K</th>
<th>71K</th>
<th>46K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response</td>
<td>0, D 29</td>
<td>.06K, D 42</td>
<td>0, D 50</td>
<td>0.1K, D 22</td>
<td>0, D 15</td>
<td>0, D 57</td>
<td>0, D 51</td>
</tr>
</tbody>
</table>

- Comparable results with imatinib with CML-blast crisis
  - 31% HEME RESPONSE (8% CR, 18% RTC, 4% NEL)

Stone et al, Blood, 2005
Study 2104: Single Agent Midostaurin Induces Blast Reduction But Not CR

<table>
<thead>
<tr>
<th>Response</th>
<th>75 mg TID FLT3mut n=20</th>
<th>50 or 100 mg BID FLT3mut n=35</th>
<th>50 or 100 mg BID FLT3wt n=57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0/20</td>
<td>0/35</td>
<td>0/57</td>
</tr>
<tr>
<td>Partial response</td>
<td>1/20</td>
<td>1/35</td>
<td>0/57</td>
</tr>
<tr>
<td>50% PB blast or BM reduction</td>
<td>14/20 (70%)</td>
<td>25/35 (71%)</td>
<td>24/57 (42%)</td>
</tr>
<tr>
<td></td>
<td>[67% for 50 mg BID &amp; 76% for 100 mg BID]</td>
<td></td>
<td>[50% for 50 mg BID &amp; 33% for 100 mg BID]</td>
</tr>
</tbody>
</table>

Generally well tolerated

Nausea/vomiting, diarrhea, and fatigue

< 10% of patients experienced grade 2 or grade 3 events at doses ≤ 100 mg/day

Hematologic toxicity was uncommon

Fischer et al, *JCO*, 2010
PKC412 plus chemo in newly diagnosed, previously untreated AML: Treatment Plan

- Induction Chemotherapy
  - DNR 60 mg/m² d1, 2, 3 plus ara-C 100 mg/m² IVCI d1-7

- Post-remission chemotherapy
  - ara-C 3 gm/m² over 3h q 12h d1, 3, and 5 x 3 cycles

- PKC412
  - 100 mg po bid begin d1 (simultaneous) OR d8 (sequential) of each cycle
  - give continuously during induction and post-CR
Study Induction Scheme by Cohort

PKC412 dosed bid

Dauno 60mg/sqm i.v.

DDD
ara-C 100mg/sqm c.i.v.

Continuous 100mg*

7 pts
8 pts

14-day treatment 100mg*

7 pts
8 pts

14-day treatment 50mg+

20 pts

20 pts

*AE rate, dt GI tox too high

28-day cycle
Efficacy

- 80% Complete Response (CR) rate (32/40)
- 92% of FLT3mut patients had a CR
- Trend toward higher CR in FLT3mut patients
- No significant difference in response rates or duration of remission between the sequential and concomitant schedules

90% CR rate also w/ soraf+IA; Ravandi et al. JCO, 2010

Response Rate in Patients with FLT3wt and FLT3mut
Similar Survival Seen in Previously Untreated Patients With FLT3mut and FLT3wt Blasts

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Med OS, mo (range)</th>
<th>Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITD (n=9)</td>
<td>20 (4-56)</td>
<td>3</td>
</tr>
<tr>
<td>TKD (n=4)</td>
<td>50 (39-54)</td>
<td>4</td>
</tr>
</tbody>
</table>

Stone, Leukemia, 2012
CALGB 10603: Prospective Phase III, double-blinded randomized study of induction and consolidation +/- Midostaurin (PKC412) in newly diagnosed patients < 60 years old with FLT3 mutated AML

Study drug is given on Days 8-21 after each course of chemotherapy, and Days 1-28 (note change) of each 28 day Maintenance cycle.

FLT3 WILD TYPE

Not on STUDY:

PKC412 MAINTENANCE
12 months

PLACEBO MAINTENANCE
12 months

DNR ARA-C PKC412

DNR ARA-C PLACEBO

CR HiDAC PKC412 X 4

CR HiDAC PLACEBO X 4
Key Eligibility Criteria

• Age 18-60, normal end-organ function
• Documented AML (non-APL)
• \(FLT3\) mutation centrally determined prior to enrollment
  – Assessed at one of 9 academic labs around the world
  – Results within 48h
• Up to 5 days of hydroxyurea allowed prior to start of treatment while awaiting results of mutation analysis
# Protocol Therapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Drug(s)</th>
<th>Dose/Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td>daunorubicin</td>
<td>60 mg/m² IVP days 1-3</td>
</tr>
<tr>
<td>(2nd cycle given based on d21 marrow)</td>
<td>cytarabine</td>
<td>200 mg/m²/d d 1-7 via IVCI</td>
</tr>
<tr>
<td></td>
<td>midostaurin</td>
<td>50 mg po bid days 8-21</td>
</tr>
<tr>
<td></td>
<td>or placebo</td>
<td></td>
</tr>
<tr>
<td><strong>Consolidation</strong></td>
<td>cytarabine</td>
<td>3 gm/m² over 3h q 12h days 1, 3, and 5</td>
</tr>
<tr>
<td>(up to 4 cycles)</td>
<td>midostaurin</td>
<td>50 mg po bid days 8-21</td>
</tr>
<tr>
<td></td>
<td>or placebo</td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>midostaurin</td>
<td>50 mg po bid days 1-28 x 12 cycles</td>
</tr>
<tr>
<td></td>
<td>or placebo</td>
<td></td>
</tr>
</tbody>
</table>

- Transplant not specifically mandated

## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>MIDO (N = 360)</th>
<th>PBO (N = 357)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median (range)</strong></td>
<td>47.1 (19.0-59.8)</td>
<td>48.6 (18.0-60.9)</td>
<td>.27</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td>.045</td>
</tr>
<tr>
<td>Female</td>
<td>187 (51.9%)</td>
<td>212 (59.4%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>173 (48.1%)</td>
<td>145 (40.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>FLT3 stratification Groups</strong></td>
<td></td>
<td></td>
<td>.995</td>
</tr>
<tr>
<td><em>FLT3 TKD (No ITD)</em></td>
<td>81 (22.5%)</td>
<td>81 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>ITD allelic ratio &lt;0.7 (+/- FLT3 TKD)</td>
<td>171 (47.5%)</td>
<td>170 (47.6%)</td>
<td></td>
</tr>
<tr>
<td>ITD allelic ratio ≥0.7 (+/- FLT3 TKD)</td>
<td>108 (30.0%)</td>
<td>106 (29.7%)</td>
<td></td>
</tr>
</tbody>
</table>

MIDO, midostaurin
Activated May 2008; completed accrual: Oct 2011 Screened 3279 patients

Total $FLT3(+)$: N = 887 (27% of screened)

Total randomized: N = 717 (81% of $FLT3(+)$)

Midostaurin (MIDO), N = 360
Induction 1, N = 355
Induction 2, N = 81
Consolidation, N = 231
Maintenance, N = 120

Placebo (PBO), N = 357
Induction 1, N = 354
Induction 2, N = 101
Consolidation, N = 210
Maintenance, N = 85

### Complete Response Rates

<table>
<thead>
<tr>
<th></th>
<th>MIDO  (N = 360)</th>
<th>PBO  (N = 357)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR by day 60</strong></td>
<td>212</td>
<td>191</td>
<td>.15</td>
</tr>
<tr>
<td><strong>Rate</strong></td>
<td>59%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td><strong>Time to CR, median (range)</strong></td>
<td>35 days (20-60)</td>
<td>35 days (20-60)</td>
<td></td>
</tr>
<tr>
<td><strong>CR in induction/consolidation</strong></td>
<td>239</td>
<td>211</td>
<td></td>
</tr>
<tr>
<td><strong>Rate</strong></td>
<td>66%</td>
<td>59%</td>
<td>.045</td>
</tr>
<tr>
<td><strong>Time to CR, median (range)</strong></td>
<td>37 days (20-99)</td>
<td>36 days (20-112)</td>
<td></td>
</tr>
</tbody>
</table>

**Includes all CRs reported within 30 days of ending protocol therapy**

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All Grade 3-4 Non-Hematologic Events, reported during treatment in ≥ 10% of patients

<table>
<thead>
<tr>
<th>Event</th>
<th>MIDO</th>
<th>PBO</th>
<th>p *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia</td>
<td>81% (n=360)</td>
<td>82% (n=357)</td>
<td>0.92</td>
</tr>
<tr>
<td>Infection</td>
<td>40%</td>
<td>38%</td>
<td>0.49</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>16%</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>13%</td>
<td>17%</td>
<td>0.17</td>
</tr>
<tr>
<td>Pain</td>
<td>13%</td>
<td>13%</td>
<td>0.91</td>
</tr>
<tr>
<td>Infection - Other</td>
<td>12%</td>
<td>12%</td>
<td>1.00</td>
</tr>
<tr>
<td>ALT, SGPT</td>
<td>12%</td>
<td>9%</td>
<td>0.23</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>13%</td>
<td>8%</td>
<td>0.02</td>
</tr>
<tr>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td>9%</td>
<td>11%</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* 2-sided Fisher’s Exact p
Grade 5 events during Treatment

**Total Deaths:** MIDO 18 (5%) vs PBO 19 (5.3%)*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Induction</th>
<th>Post Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIDO</td>
<td>PBO</td>
</tr>
<tr>
<td>Death NOS</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Hemorrhage, CNS</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Colitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Perforation, GI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Potassium serum</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16</strong></td>
<td><strong>12</strong></td>
</tr>
</tbody>
</table>

2-sided Fisher’s Exact p = 1.0
Overall Survival (Primary Endpoint)

23% Reduced Risk of Death in the MIDO Arm

- Median OS: MIDO 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months

Controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

Event-Free Survival (Key Secondary Endpoint)

- Event: first of no CR within 60 days, relapse or death
- 4 year EFS rate: MIDO 27.6% vs PBO 20.2%

* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)
Consistent Effect on EFS by *FLT3* status

<table>
<thead>
<tr>
<th>Overall (strat)</th>
<th>N</th>
<th>HR</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>717</td>
<td>0.79</td>
<td>0.66</td>
<td>0.93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FLT3-ITD-High</th>
<th>N</th>
<th>HR</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>214</td>
<td>0.77</td>
<td>0.57</td>
<td>1.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FLT3-ITD-Low</th>
<th>N</th>
<th>HR</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>341</td>
<td>0.85</td>
<td>0.67</td>
<td>1.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FLT3-TKD</th>
<th>N</th>
<th>HR</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>162</td>
<td>0.66</td>
<td>0.44</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Confidence intervals are two-sided; p-values are one-sided.

HR: Hazard Ratio, LL: Lower Limit; UL: Upper Limit;
strat: stratified by FLT3 status; ITD-low: Allelic ratio < 0.7; ITD-high: Allelic ratio ≥ 0.7
Disease-Free Survival
CR in Induction/Consolidation

- 4 year DFS rate: MIDO 46.4% vs. PBO 37.4%
- Event: first of relapse or death among CR

NE: not estimable

* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High).
Overall Survival: Post-Transplant Treatment With MIDO Increases OS After SCT in CR1

SCT in CR1
HR 0.61

SCT outside CR1
HR 0.98
Conclusions

• Midostaurin, a mult-itargeted kinase inhibitor, improves OS when added to standard chemo with one year maintenance in newly diagnosed pts aged 18-60 with ITD and TKD FLT3 mutant AML, and represents a new standard of care

• OS and EFS benefit was consistent in uncensored as well as censored analyses, despite high SCT rate

• Safety profile similar in each arm

• An international academic-industry collaborative AML study based on genotype at dx is feasible

* Patients may receive hydroxyurea during screening phase

** Optional 2\textsuperscript{nd} cycle in patients achieving PR after cycle I

*** Cytarabine: 18-65 years, 3g/m\textsuperscript{2}, q12hr, day 1,3,5; >65 years, 1g/m\textsuperscript{2}, q12hr, day 1,3,5; optional for patients before allogeneic HSCT

AML With $FLT3$-ITD
AMLSG 16-10 Compared to Historical Controls

Age 18-<60 yrs

- AMLSG 16-10 $n = 79$
- Historical-control AMLSG $N = 481$

$P = .014$

Age 60-70 yrs

- AMLSG 16-10 $n = 37$
- Historical-control AMLSG $N = 97$

$P = .036$

Midostaurin in AML: FAQs

- When will the drug be approved?
  • I don’t know; ask Novartis

- What will the approval look like?
  • Untreated mutant FLT3 age to 60, ? higher

- When will C10603/RATIFY be published
  • Second revision under review

- Is there enough data to justify adding midostaurin to all newly diagnosed mutant FLT3 AML pts who can receive 3+7?
  • YES
Midostaurin in AML: Final Points

- Midostaurin plus chemo leads to a lower death rate than chemo alone in initial rx of mutant FLT3 AML
  - Is benefit due to FLT3 inhibition at all or in part?
  - Chemo +/- mido in upfront FLT 3 WT AML trial planned
- Will also be approved in aggressive systemic mastocytosis
- SWOG trial will test azacitididine +/- mido in chemo unfit older AML
Many thought C10603 would be negative

Many thought the Pats would lose when down by 25 in third quarter.
Acknowledgements

• DFCI Adult Leukemia Team
  – MDs: DeAngelo, Garcia, Steensma, Wadleigh, Luskin, Winer
  – MD Scientists: Abel, DeCaprio, Ebert, Frank, Griffin, Lane, Letai, Lindsley, Weinstock
  – Midlevel practitioners: Galinsky, Cahill, Edmonds, Gerard, Penicaud
  – Research RN Toomey-Matthews, CRCs, administrative support

• Other Key Local Colleagues
  – DFCI SCT: Alyea, Antin, Cutler, Ho, Koreth, Soiffer
  – DFHCC (MGH): Amrein, Fathi, Graubert, Hobbs
  – DFHCC (BIDMC): Avigan, Rosenblatt

National and International (partial list) (Novartis)
  Dohner, Fischer, Larson, Marcucci, Schiffer, CTEP/NCI
Design considerations

• Primary Endpoint: Overall Survival, not censoring for transplantation

• Sample size: 714 evaluable patients
  – HR = 0.78 for OS
  – Power = 84%
  – Type I error rate = 0.025 (1-sided)
  – Final analysis after 509 events (deaths) observed
  – Interim analysis conducted at 50% of events
Revised Analysis Plan

• Alliance DSMB and CTEP approved the primary analysis of OS to occur with a cut off of April 1, 2015 with 357 events
  • Event rate reached a plateau: 6 events 2014, 3 in 2015.
    – 509 events predicted to occur in 2025
  • Higher than expected transplant rate: 25% in CR 1, 57% overall
  • increased TKD incidence: 23%
  • Median follow-up time for survivors: 56.7 mo (range: 0.1, 79.2 mo)

• Critical value to declare statistical significance: 0.0239 (1-sided).
Event-Free Survival
CR in Induction/Consolidation

<table>
<thead>
<tr>
<th></th>
<th>MIDO</th>
<th>PBO</th>
<th>1-sided Log-rank p-value*</th>
<th>Hazard Ratio MIDO vs. PBO (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>360</td>
<td>357</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of events</td>
<td>242</td>
<td>271</td>
<td>0.0002</td>
<td>0.73 (0.61, 0.87)</td>
</tr>
<tr>
<td>Median (mo)</td>
<td>11.3</td>
<td>6.1</td>
<td>(8.4, 15.1)</td>
<td>(4.7, 7.5)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*controlled for FLT3 subtype (TKD, ITD-Low, ITD-High).

- Event: first of either no CR in induction/consolidation, or relapse or death
### FLT 3 inhibitors in prior studies

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>IC$_{50}$ (medium)$^a$</th>
<th>IC$_{50}$ (plasma)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lestaurtinib</td>
<td>2 nM</td>
<td>700 nM</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>6 nM</td>
<td>~1000 nM</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>3 nM</td>
<td>~265 nM</td>
</tr>
<tr>
<td>Quizartinib</td>
<td>1 nM</td>
<td>18 nM</td>
</tr>
</tbody>
</table>

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**a** – Molm-14 cells incubated in RPMI/10% FBS

**b** – Molm-14 cells incubated in plasma


Human kinome image generated using TREEspot™ software tool and reprinted with permission from KINOMEScan™, a division of DiscoveRx Co.